



CASE 4-32618A/VSR

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF  
ET AL.

Art Unit: 1627

Examiner: GARCIA, MAURIE E.

APPLICATION NO: 09/248,158

FILED: FEBRUARY 9, 1999

FOR: DIRECT ADSORPTION SCINTILLATION ASSAY FOR MEASURING  
ENZYME ACTIVITY AND ASSAYING BIOCHEMICAL PROCESSES

**MS: Appeal Brief- Patents**  
Commissioner for Patents  
PO Box 1450  
Alexandria, VA 22313-1450

BRIEF FOR APPELLANTS

Sir:

I. Real Party in Interest

Vicuron Pharmaceuticals of 34790 Ardentech Court, Fremont, CA 94555 is the owner of the entire right, title and interest to the invention described in the patent application. The inventor assigned their interest in the application to Versicor Inc. The company, Versicor Inc., merged with Biosearch Italia S.p.A. on February 28, 2003 and on March 26, 2003 the name of the merged company was changed to Vicuron Pharmaceuticals.

II. Related Appeals and Interferences

There are no related appeals or interferences.

III. Status of Claims

Claims 1, 3, 5-10 and 19 stand rejected, are the claims on appeal, and are listed in Appendix A. Claims 11-18 and 20 are still pending, but have been withdrawn from consideration and are listed in Appendix B. Claim 2 was cancelled in an amendment dated November 20, 2000. Claims 29-46 were cancelled as an amendment dated February 16, 2001. Claim 4 was

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cancelled in an amendment dated October 25, 2001. Claims 21-28 were cancelled in an amendment dated September 9, 2002.

#### IV. Status of Amendments

Amendments to Claims 1 and 20 were made in an Amendment After Final Rejection dated July 18, 2003, but these amendments were refused entry in an Advisory Action dated August 5, 2003. Appellants petitioned to have the Amendment After Final Rejection entered. In a Decision on Petition dated March 18, 2004, Appellants' petition was granted. Therefore, the claims listed in Appendices A and B incorporate the Amendment After Final Rejection.

#### V. Summary of Invention

The present invention is directed to a direct adsorption scintillation assay wherein the reaction product of a chemical or biochemical transformation binds to scintillating material to produce a signal above background. The progress or degree of completion of the molecular transformation, e.g., an enzymatic transformation, is monitored by measuring the amount of scintillation.

#### VI. Issues

Whether Claims 1, 3, 5 -10 and 19 are obvious under 35 U.S.C. §103(a) over Kasila et al. (U.S. patent no. 5,972,595) in view of Brown et al. (FlashPlate Technology. 1997. High Throughput Screening, Editor: Devlin, J.P., NY, NY pp. 317 - 328).

#### VII. Grouping of Claims

The appealed claims stand or fall together.

#### VIII. Argument

Claims 1, 3, 5 - 10 and 19 are not obvious over Kasila et al. and Brown et al.

In the Final Rejection it is stated:

"Kasila et al teach a method for measuring enzyme activity using a solid support coated with a hydrophobic layer (see column 2, lines 10-23). Specifically, the solid supports are 96-well Flashplates™ (which are a scintillating material; see definition, column 2, lines 48-50) coated with an artificial lipid layer in various ways (see, for example, column 4, lines 25-38 and column 5, line 63 through column 6, line 22). Enzyme substrates are bound via hydrophobic interactions within the lipid layer (column 3, lines 26-39). The biochemical transformation of the bound substrate

causes a cleavage of a portion of the molecule, thus rendering it hydrophilic (see patented claims, especially claim 1). The hydrophilic portion is washed away, thus reducing the level of scintillation (see, for example, column 5, lines 36-60). The assay of Kasila et al can be used to study various enzymes and is designed to study them in high-throughput fashion (column 6, lines 24-60).

Kasila et al lacks the specific teaching of where the 'reaction product of the chemical or biochemical transformation binds to the scintillating material' to produce a signal above background. The reference teaches the opposite scenario (reaction product is washed away, thus reducing the level of scintillation); however, the reference teaches that a variety of enzyme assays can be conducted using their methodology with different method steps, enzymes, labels and solid supports (see column 3, line 25 – column 4, line 19). For example, Kasila et al teach that the 'enzyme activity can be measured by detecting the reporter label fragments in the aqueous material' (column 4, lines 8-9). Importantly, Kasila et al teach 'the use of a substrate that allows the study of enzyme activity in samples without the need to extract the reaction products' and that '[w]ith appropriate substrate design' their invention 'can be used to study a variety of enzymes...for which the assay methods otherwise require extraction steps' (column 3, lines 10-25). Thus, it is the examiner's position that Kasila et al teach the general conditions of the instant claims and to modify the teachings of the reference where the 'reaction product of the chemical or biochemical transformation binds to the scintillating material' to produce a signal above background would be obvious to one of ordinary skill. '[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.' *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

Moreover, the binding of radioactive elements to scintillating material in an enzyme assay was well established in the art at the time of filing. For example, Brown et al teach the advantages of using the microplate surface scintillation effect in general (page 317), and for enzyme assays in particular (Section IV, beginning on page 321). These offer the opportunity to save time and cut costs (see Section VI, Summary, page 327).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to use the method of Kasila et al where the 'reaction product of the chemical or biochemical transformation binds to the scintillating material' to produce a signal above background. The motivation is two-fold: (1) because the general conditions of a claim are disclosed in Kasila, it is not inventive to discover the optimum or workable ranges by routine experimentation (*In re Aller*, cited above); also (2) since the binding of radioactive elements to scintillating material in an enzyme assay was well established in the art at the time of filing (as evidenced by Brown et al), it would have been obvious to one of ordinary skill that this format was a desirable one for enzyme assays. Brown teaches that such assays save time and cut costs (see above). Also, Kasila et al teach that '[w]ith appropriate substrate design' their invention 'can be used to study

a variety of enzymes...for which the assay methods otherwise require extraction steps' and that the 'particular substrate to use is designed or selected for its susceptibility to the action of the enzyme and an appropriate location for the label' (column 3, lines 10-25)."

In the Final Rejection, it is acknowledged that the Kasila et al. reference lacks the specific teaching of where the reaction product of the chemical or biochemical transformation binds to the scintillating material to produce a signal above background (which necessarily results in increased scintillation being correlated with the progression of the reaction). It is further acknowledged in the Final Rejection that Kasila et al. teach the opposite scenario, i.e., where reaction product is washed away, thus reducing the level of scintillation.

It is held in the Final Rejection that the Kasila et al. reference teaches the general conditions of the instant claims and thus it would be obvious to one of ordinary skill in the art to modify the teachings of Kasila et al. to arrive at Appellants' invention. Brown et al. is cited to teach the advantages of using the microplate surface scintillation effect; however, this would appear to add little, if anything, to Kasila et al. because Kasila et al. also teach use of microplates in their assay.

It is respectfully submitted that requiring the exact "opposite scenario" is not merely a modification of reaction conditions, but rather, is a fundamental change of the assay itself. There is absolutely nothing in either Kasila et al. or Brown et al. that teaches or suggests Appellants' claimed invention which requires the reaction product to be bound to the scintillation material.

Also, Kasila et al. requires that the substrate must be immobilized on a solid support prior to interaction with an enzyme. The immobilized form of the substrate is not the same as the natural form of the substrate and is therefore not ideal as it can have a different conformation. In contrast, in Appellants' assay the substrate is not bound to a solid support and is therefore much more suitable to evaluate transformations, e.g., enzymatic transformations.

The Examiner cites *In re Aller*, 105 USPQ 233 (C.C.P.A. 1955) to support the rejection. It is respectfully submitted that the facts of *In re Aller* are non-analogous to the present invention. The process sought to be patented in *In re Aller* differed from the prior art only in reciting a different temperature and concentration of a reactant. In marked contrast, Appellants' assay is fundamentally different from the prior art, it is not merely a change in reaction conditions over the prior art, such as a change in temperature or a change in concentration of reactants. Moreover, even the C.C.P.A. acknowledged that such changes, i.e., temperature and concentration, may under certain circumstances impart patentability to an invention (*In re Aller* at 235).

Even if one skilled in the art had both Kasila et al. and Brown et al. before him, he still would not arrive at Appellants' invention. The references fail not only to expressly disclose Appellants' claimed invention, but also fail to suggest to one of ordinary skill in the art modifications needed to meet all the claim limitations (see *Litton Industrial Product, Inc. v. Solid State Systems, Corp.*, 225 USPQ 34, 38 (Fed. Cir. 1985)).

There is not even the remotest hint in either cited reference to suggest the modifications necessary to arrive at Appellants' claimed assay. It is submitted that the only way a skilled artisan would be motivated to modify the cited references to arrive at Appellants' assay would be to use Appellants' own teachings as a guide. As is well settled, using Appellants' own disclosure as a ground to make an obviousness rejection is a classic example of using impermissible hindsight reconstruction. See *In re Spinnable*, 160 USPQ 237 (CCPA 1969).

In the Final Rejection there is a section titled "Response to Arguments". Appellants will address below the specific points raised in the section.

Paragraphs 9-11 of the Final Rejection are rendered moot by the granting of Appellants' petition, thus allowing the amendment in Claim 1 from the phrase "can be stimulated" to "is stimulated".

Paragraph 12 of the Final Rejection states:

"12. Applicant argues on page 2 of the Response that the method of Kasila and Brown would need to be fundamentally changed to result in the method of the claimed invention and that the references 'fail to suggest to one of ordinary skill in the art modifications needed to meet all claim limitations'. The examiner respectfully disagrees. Although Kasila specifically teaches washing the reaction product away, thus reducing the level of scintillation, the reference also teaches that a variety of enzyme assays can be conducted using their methodology with different method steps, enzymes, labels and solid supports (see column 3, line 25 – column 4, line 19). For example, Kasila et al teach that the 'enzyme activity can be measured by detecting the reporter label fragments in the aqueous material' (column 4, lines 8-9). Importantly, Kasila et al teach "the use of a substrate that allows the study of enzyme activity in samples without the need to extract the reaction products" and that '[w]ith appropriate substrate design' their invention 'can be used to study a variety of enzymes...for which the assay methods otherwise require extraction steps' (column 3, lines 10-25)."

Regarding paragraph 12 of the Final Rejection, Appellants reiterate their position that the methods of Kasila et al. and Brown et al. would need to be fundamentally changed in order to arrive at Appellants' claimed method. As pointed out above, assuming *arguendo*, that the combination of Kasila et al. and Brown et al. is valid, the combination still does not teach or

suggest Appellants' claimed method. That is, one skilled in the art having both Kasila et al. and Brown et al. before him, still would not arrive at Appellants' invention.

Paragraph 13 of the Final Rejection states:

"13. Also, the examiner pointed to Brown for teachings of the advantages of using the microplate surface scintillation effect in general (page 317), and for enzyme assays in particular (Section IV, beginning on page 321). When one looks to the enzyme assays in Section IV of Brown, it is clear that a variety of formats are taught; see e.g. page 325, 1<sup>st</sup> paragraph, which *describes an assay that shows that 'increased scintillation correlates with the progression of the reaction'.*"

Regarding paragraph 13 of the Office Action, it is acknowledged that at Page 325, first paragraph, Brown et al. describes an assay that shows that increased scintillation correlates with the progression of the reaction. However, this teaching of Brown et al. is of little relevance regarding the patentability of Appellants' invention. In the assay described on Page 325, first paragraph, of Brown et al. a reactant, i.e., the biotinylated oligonucleotide, "is attached to a streptavidin coated FlashPlate". The binding in Brown et al. requires modification of the substrate (attachment of biotin) and the binding requires a receptor-ligand interaction (streptavidin-biotin).

In marked contrast, Appellants' method requires that "the absorption of the molecular species to the scintillation material is due to a chemical or biochemical transformation of one of said molecular species into another of said molecular species". Furthermore, Appellants' assay avoids the need to attach an additional chemical moiety to the substrate which results in a more desirable assay. Moreover, the binding in Appellants' assay is not a receptor-ligand specific interaction as required in Brown et al., but rather the binding in Appellants' assay is a "general molecular property-based binding interaction". Thus, Brown et al.'s method is fundamentally different from Appellants' claimed method and there is not a hint of guidance in either Brown et al. or Kasila et al. to make the modifications necessary to arrive at Appellants' method.

Paragraphs 14-16 of the Final Rejection state:

"14. Importantly, the interpretation of the claims in light of the specification should be considered. The instant specification states that a wide variety of formats are contemplated for the interaction of substrate and product, including several examples that would result in decreased scintillation as the reaction progresses (see page 17, lines 1-17). There is at least one assay specifically set forth in the specification that results in decreased scintillation as the reaction progresses, see page 18, lines 9-17, directed to a phosphatase reaction. See also page 16, lines 21-23. However, the instant claims are not limited in any way to a particular reaction, particular surface of the scintillating material or particular "molecular property based binding interaction".

Dependent claims 3 and 9 would cover **both** assay scenarios where increased or decreased scintillation could be seen.

15. Most importantly, although dependent claim 20 is currently withdrawn from consideration, it should be noted that this claim specifically recites phosphatase catalyzed reactions. As described in paragraph 14 above, these reactions are specifically described in the instant specification, to result in decreased scintillation as the reaction progresses, see page 18, lines 9-17.

16. Thus the instant claims do not have the necessary specificity (i.e. do not contain limitations) for the particular reaction, particular surface of the scintillating material and/or particular 'molecular property-based binding interaction' and are not limited to scenarios where increased scintillation correlates with the progression of the reaction. In fact, the instant claims appear to encompass scenarios where either increased or decreased scintillation could be seen (see paragraphs 14 & 15 above). As stated in the rejection, since the binding of radioactive elements to scintillating material in an enzyme assay was well established in the art at the time of filing (as evidenced by Brown et al), it would have been obvious to one of ordinary skill that this format was a desirable one for enzyme assays. Brown teaches that such assays save time and cut costs (see rejection). Also, Kasila et al teach that '[w]ith appropriate substrate design' their invention 'can be used to study a variety of enzymes...for which the assay methods otherwise require extraction steps' and that the 'particular substrate to use is designed or selected for its susceptibility to the action of the enzyme and an appropriate location for the label' (column 3, lines 10-25)."

Regarding paragraph 14 of the Final Rejection Appellants are not claiming an assay that results in decreased scintillation being correlated with reaction progression. Claim 10 was previously amended during prosecution to delete phosphatase catalyzed reactions and protease catalyzed reactions. The comments regarding Claim 20 in paragraph 14 are not understood. Claim 20 has been withdrawn from consideration and is not on appeal. Nevertheless, Claim 20 was amended in Appellants' Amendment After Final Rejection to delete the same reactions deleted in Claim 10.

The comments regarding Claims 3 and 9 in the last section of paragraph 14 are manifestly incorrect since both Claims 3 and 9 are dependent on Claim 1. These dependent claims have all of the limitations of Claim 1 and, therefore, it is impossible for any of these claims to read on an assay where decreased scintillation correlated with reaction progression can be seen.

Specifically, regarding paragraphs 15 and 16 of the Final Rejection, as stated above, it is impossible for Appellants' claimed method to cover scenarios where decreased scintillation is correlated with reaction progression. Whether or not increased scintillation is explicitly stated in the claims is irrelevant because increased scintillation is the only thing that can occur in

Appellants' method. That is, increased scintillation is inherent, it is a consequence of performing Appellants' claimed assay.

Paragraph 17 of the Final Rejection states:

"17. Lastly, in response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning (Response, page 2, bottom), it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). The examiner maintains that the combined teachings of the cited references indicate information that was within the level of ordinary skill and render the claimed invention *prima facie* obvious."

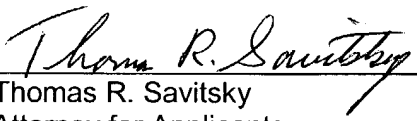
Regarding paragraph 17, Appellants reiterate that the obviousness rejection is based on impermissible hindsight reconstruction. The only way one skilled in the art would arrive at Appellants' method, even having Kasila et al. and Brown et al. before him, would be to use Appellants' own disclosure as a guide. There is nothing in either Kasila et al. or Brown et al. that teaches or suggests Appellants' claimed method.

All of the new points raised in the Advisory Action are believed to be rendered moot by the Decision on Petition of March 18, 2004.

In light of the above remarks, Appellants respectfully request reversal of the rejection of Claims 1, 3, 5-10 and 19 under 35 U.S.C. §103(a).

Respectfully submitted,

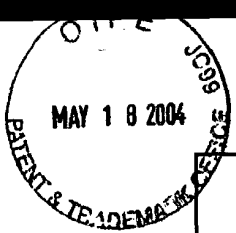
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Encl.: Appendix

Date: May 18, 2004



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V. Summary of Invention

The present invention is directed to a direct adsorption scintillation assay wherein the reaction product of a chemical or biochemical transformation binds to scintillating material to produce a signal above background. The progress or degree of completion of the molecular transformation, e.g., an enzymatic transformation, is monitored by measuring the amount of scintillation.

VI. Issues

Whether Claims 1, 3, 5 -10 and 19 are obvious under 35 U.S.C. §103(a) over Kasila et al. (U.S. patent no. 5,972,595) in view of Brown et al. (FlashPlate Technology. 1997. High Throughput Screening, Editor: Devlin, J.P., NY, NY pp. 317 - 328).

VII. Grouping of Claims

The appealed claims stand or fall together.

VIII. Argument

Claims 1, 3, 5 - 10 and 19 are not obvious over Kasila et al. and Brown et al.

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"Kasila et al teach a method for measuring enzyme activity using a solid support coated with a hydrophobic layer (see column 2, lines 10-23). Specifically, the solid supports are 96-well Flashplates™ (which are a scintillating material; see definition, column 2, lines 48-50) coated with an artificial lipid layer in various ways (see, for example, column 4, lines 25-38 and column 5, line 63 through column 6, line 22). Enzyme substrates are bound via hydrophobic interactions within the lipid layer (column 3, lines 26-39). The biochemical transformation of the bound substrate

causes a cleavage of a portion of the molecule, thus rendering it hydrophilic (see patented claims, especially claim 1). The hydrophilic portion is washed away, thus reducing the level of scintillation (see, for example, column 5, lines 36-60). The assay of Kasila et al can be used to study various enzymes and is designed to study them in high-throughput fashion (column 6, lines 24-60).

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Moreover, the binding of radioactive elements to scintillating material in an enzyme assay was well established in the art at the time of filing. For example, Brown et al teach the advantages of using the microplate surface scintillation effect in general (page 317), and for enzyme assays in particular (Section IV, beginning on page 321). These offer the opportunity to save time and cut costs (see Section VI, Summary, page 327).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to use the method of Kasila et al where the 'reaction product of the chemical or biochemical transformation binds to the scintillating material' to produce a signal above background. The motivation is two-fold: (1) because the general conditions of a claim are disclosed in Kasila, it is not inventive to discover the optimum or workable ranges by routine experimentation (*In re Aller*, cited above); also (2) since the binding of radioactive elements to scintillating material in an enzyme assay was well established in the art at the time of filing (as evidenced by Brown et al), it would have been obvious to one of ordinary skill that this format was a desirable one for enzyme assays. Brown teaches that such assays save time and cut costs (see above). Also, Kasila et al teach that '[w]ith appropriate substrate design' their invention 'can be used to study

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It is respectfully submitted that requiring the exact "opposite scenario" is not merely a modification of reaction conditions, but rather, is a fundamental change of the assay itself. There is absolutely nothing in either Kasila et al. or Brown et al. that teaches or suggests Appellants' claimed invention which requires the reaction product to be bound to the scintillation material.

Also, Kasila et al. requires that the substrate must be immobilized on a solid support prior to interaction with an enzyme. The immobilized form of the substrate is not the same as the natural form of the substrate and is therefore not ideal as it can have a different conformation. In contrast, in Appellants' assay the substrate is not bound to a solid support and is therefore much more suitable to evaluate transformations, e.g., enzymatic transformations.

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Even if one skilled in the art had both Kasila et al. and Brown et al. before him, he still would not arrive at Appellants' invention. The references fail not only to expressly disclose Appellants' claimed invention, but also fail to suggest to one of ordinary skill in the art modifications needed to meet all the claim limitations (see *Litton Industrial Product, Inc. v. Solid State Systems, Corp.*, 225 USPQ 34, 38 (Fed. Cir. 1985)).

There is not even the remotest hint in either cited reference to suggest the modifications necessary to arrive at Appellants' claimed assay. It is submitted that the only way a skilled artisan would be motivated to modify the cited references to arrive at Appellants' assay would be to use Appellants' own teachings as a guide. As is well settled, using Appellants' own disclosure as a ground to make an obviousness rejection is a classic example of using impermissible hindsight reconstruction. See *In re Spinnable*, 160 USPQ 237 (CCPA 1969).

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"12. Applicant argues on page 2 of the Response that the method of Kasila and Brown would need to be fundamentally changed to result in the method of the claimed invention and that the references 'fail to suggest to one of ordinary skill in the art modifications needed to meet all claim limitations'. The examiner respectfully disagrees. Although Kasila specifically teaches washing the reaction product away, thus reducing the level of scintillation, the reference also teaches that a variety of enzyme assays can be conducted using their methodology with different method steps, enzymes, labels and solid supports (see column 3, line 25 – column 4, line 19). For example, Kasila et al teach that the 'enzyme activity can be measured by detecting the reporter label fragments in the aqueous material' (column 4, lines 8-9). Importantly, Kasila et al teach "the use of a substrate that allows the study of enzyme activity in samples without the need to extract the reaction products" and that '[w]ith appropriate substrate design' their invention 'can be used to study a variety of enzymes...for which the assay methods otherwise require extraction steps' (column 3, lines 10-25)."

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Regarding paragraph 13 of the Office Action, it is acknowledged that at Page 325, first paragraph, Brown et al. describes an assay that shows that increased scintillation correlates with the progression of the reaction. However, this teaching of Brown et al. is of little relevance regarding the patentability of Appellants' invention. In the assay described on Page 325, first paragraph, of Brown et al. a reactant, i.e., the biotinylated oligonucleotide, "is attached to a streptavidin coated FlashPlate". The binding in Brown et al. requires modification of the substrate (attachment of biotin) and the binding requires a receptor-ligand interaction (streptavidin-biotin).

In marked contrast, Appellants' method requires that "the absorption of the molecular species to the scintillation material is due to a chemical or biochemical transformation of one of said molecular species into another of said molecular species". Furthermore, Appellants' assay avoids the need to attach an additional chemical moiety to the substrate which results in a more desirable assay. Moreover, the binding in Appellants' assay is not a receptor-ligand specific interaction as required in Brown et al., but rather the binding in Appellants' assay is a "general molecular property-based binding interaction". Thus, Brown et al.'s method is fundamentally different from Appellants' claimed method and there is not a hint of guidance in either Brown et al. or Kasila et al. to make the modifications necessary to arrive at Appellants' method.

Paragraphs 14-16 of the Final Rejection state:

"14. Importantly, the interpretation of the claims in light of the specification should be considered. The instant specification states that a wide variety of formats are contemplated for the interaction of substrate and product, including several examples that would result in decreased scintillation as the reaction progresses (see page 17, lines 1-17). There is at least one assay specifically set forth in the specification that results in decreased scintillation as the reaction progresses, see page 18, lines 9-17, directed to a phosphatase reaction. See also page 16, lines 21-23. However, the instant claims are not limited in any way to a particular reaction, particular surface of the scintillating material or particular "molecular property based binding interaction".

Dependent claims 3 and 9 would cover **both** assay scenarios where increased or decreased scintillation could be seen.

15. Most importantly, although dependent claim 20 is currently withdrawn from consideration, it should be noted that this claim specifically recites phosphatase catalyzed reactions. As described in paragraph 14 above, these reactions are specifically described in the instant specification, to result in decreased scintillation as the reaction progresses, see page 18, lines 9-17.

16. Thus the instant claims do not have the necessary specificity (i.e. do not contain limitations) for the particular reaction, particular surface of the scintillating material and/or particular 'molecular property-based binding interaction' and are not limited to scenarios where increased scintillation correlates with the progression of the reaction. In fact, the instant claims appear to encompass scenarios where either increased or decreased scintillation could be seen (see paragraphs 14 & 15 above). As stated in the rejection, since the binding of radioactive elements to scintillating material in an enzyme assay was well established in the art at the time of filing (as evidenced by Brown et al), it would have been obvious to one of ordinary skill that this format was a desirable one for enzyme assays. Brown teaches that such assays save time and cut costs (see rejection). Also, Kasila et al teach that '[w]ith appropriate substrate design' their invention 'can be used to study a variety of enzymes...for which the assay methods otherwise require extraction steps' and that the 'particular substrate to use is designed or selected for its susceptibility to the action of the enzyme and an appropriate location for the label' (column 3, lines 10-25)."

Regarding paragraph 14 of the Final Rejection Appellants are not claiming an assay that results in decreased scintillation being correlated with reaction progression. Claim 10 was previously amended during prosecution to delete phosphatase catalyzed reactions and protease catalyzed reactions. The comments regarding Claim 20 in paragraph 14 are not understood. Claim 20 has been withdrawn from consideration and is not on appeal. Nevertheless, Claim 20 was amended in Appellants' Amendment After Final Rejection to delete the same reactions deleted in Claim 10.

The comments regarding Claims 3 and 9 in the last section of paragraph 14 are manifestly incorrect since both Claims 3 and 9 are dependent on Claim 1. These dependent claims have all of the limitations of Claim 1 and, therefore, it is impossible for any of these claims to read on an assay where decreased scintillation correlated with reaction progression can be seen.

Specifically, regarding paragraphs 15 and 16 of the Final Rejection, as stated above, it is impossible for Appellants' claimed method to cover scenarios where decreased scintillation is correlated with reaction progression. Whether or not increased scintillation is explicitly stated in the claims is irrelevant because increased scintillation is the only thing that can occur in

Appellants' method. That is, increased scintillation is inherent, it is a consequence of performing Appellants' claimed assay.

Paragraph 17 of the Final Rejection states:

"17. Lastly, in response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning (Response, page 2, bottom), it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). The examiner maintains that the combined teachings of the cited references indicate information that was within the level of ordinary skill and render the claimed invention *prima facie* obvious."

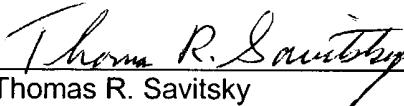
Regarding paragraph 17, Appellants reiterate that the obviousness rejection is based on impermissible hindsight reconstruction. The only way one skilled in the art would arrive at Appellants' method, even having Kasila et al. and Brown et al. before him, would be to use Appellants' own disclosure as a guide. There is nothing in either Kasila et al. or Brown et al. that teaches or suggests Appellants' claimed method.

All of the new points raised in the Advisory Action are believed to be rendered moot by the Decision on Petition of March 18, 2004.

In light of the above remarks, Appellants respectfully request reversal of the rejection of Claims 1, 3, 5-10 and 19 under 35 U.S.C. §103(a).

Respectfully submitted,

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TRS/ld

Encl.: Appendix

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